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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/759,416	01/16/2004	Aseem Z. Ansari	09820.265	8742

25005 7590 08/06/2009

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ART UNIT	PAPER NUMBER
1636	

NOTIFICATION DATE	DELIVERY MODE
08/06/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/759,416	ANSARI, ASEEM Z.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6-10,13,15-19,22,24-28,31,32,34-36 and 38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6-10,13,15-19,22,24-28,31,32,34-36 and 38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 April 2009* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the amendment, filed 4/9/2009, in which claim 4 was canceled, and claims 1, 10, 13, 16, 17, 19, 22, 25, 26, 28, 31, 32, 34-36 and 38 were amended. Claims 1-3, 6-10, 13, 15-19, 22, 24-28, 31, 32, 34-36 and 38 are pending and under consideration.

Applicant's arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

Specification

The disclosure is objected to because of the following informalities: the brief description of Figure 4a on page 11 does not provide a sequence identifier for the sequence disclosed in the figure. Where the description or claims of a patent application discuss a sequence that is set forth in the Sequence Listing, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application. It would be remedial to amend the brief description of Figure 4a to indicate that the Phe-Tyr-Pro-Trp-Met sequence is SEQ ID NO: 13.

Appropriate correction is required.

Response to Arguments - Claim Objections

The objection of claims 16, 17, 25, 26 and 34 has been withdrawn in view of Applicant's amendment to the claims in the reply filed 4/9/2009.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22 and 24-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection**.

In the amendment filed 4/9/2009, independent claim 22 was amended to replace the phrase "wherein the test compound is known to modulate binding of natural transcription factors to the transcription factor binding site defined in the nucleic acid target" and now recites that "the test compound is known to modulate transcription of a gene operationally linked with the sequence-specific transcription factor binding site defined in the nucleic acid target." The response states the amendment makes it clear what is accomplished by performing the method; specifically, the response states, "the recited steps determine whether the test compound alters binding of a sequence-specific transcription factor to the nucleic acid target."

As written the claim is drawn to a "method of evaluating one or more test compounds to identify test compounds that facilitate, recruit, or stabilize binding of sequence-specific transcription factors to corresponding single-, double-, or triple-stranded transcription factor binding sites on nucleic acid." Thus, the method is used to screen test compounds known to alter transcription to determine whether they alter binding of a transcription factor to the nucleic acid target. This is a new concept not supported by the original disclosure.

The response asserts that support for the amendment can be found in the specification on page 6, lines 1-7 and page 13, lines 15-18. However, these portions of the specification do not disclose testing compounds known to modulate transcription from a sequence-specific transcription factor binding site for the ability to modulate transcription factor binding to the same sequence-specific transcription factor binding site.

With regard to screening "known" test compounds, the specification envisions (i) using compounds known to interface with a natural transcription factor that binds to a nucleic acid sequence and testing the compounds for the ability to exert a similar modulatory effect on an artificial transcription factor that binds to the same nucleic acid sequence (e.g., paragraph bridging pages 7-8); and (2) using a test compound known to interact with a natural transcription factor as a means to screen putative artificial transcription factors and to measure whether a putative artificial transcription factor will bind or interface cooperatively with a natural transcription factor. The first use of "known" test compounds is consistent with the method steps recited in claims 22 and 24-28. The originally filed disclosure does not provide support for the application of the claimed method steps to determine whether a compound known to modulate transcription affects binding of a transcription factor.

The original specification, drawings and claims were thoroughly reviewed and no support could be found for the amendment. Accordingly, the amendment is a departure from the specification and claims as originally filed, and the passages that Applicant has provided do not provide support.

Response to Arguments - 35 USC § 112

The rejection of claims 10, 19, 22, 24-28, 32 and 36 under 35 U.S.C. 112, second paragraph, has been withdrawn in view of Applicant's amendment to the claims in the reply filed 4/9/2009.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 31, 34, 35 and 38 are rejected under 35 U.S.C. 102(e) as being anticipated by Stanojevic (US Patent Application Publication NO. 2003/105045). This rejection was made in the Office action mailed 10/29/2008 and has been rewritten to address the amendments to the claims in the reply filed 4/9/2009.

Regarding claims 31 and 34, Stanojevic teaches an artificial transcription factor that comprises a non-peptidic DNA binding domain, a flexible linker, and a transcriptional effector,

one end of the linker being covalently bound to the DNA binding domain, and the other end of the linker being covalently bound to the transcriptional effector (e.g., paragraph [0011]). Further, Stanojevic teaches the further inclusion of one moiety that is a spacer or anchor molecule that allows the covalent attachment of the linker to the non-peptidic DNA binding domain (e.g., paragraphs [0063] and [0066]). Stanojevic teaches the artificial transcription factor where the linker is 10-100 Å, in the range of 25-40 Å, in the range of 40-60 Å, or in the range of 60-100 Å (e.g., paragraph [0011]). The rejected claims require an isolated nucleic acid target that defines one and only one putative binding site for a sequence-specific regulatory factor, excluding binding sites for transcriptional machinery, the isolated nucleic acid target having covalently bonded thereto, at a point proximate to the binding site, one an only one anchor moiety, a linker moiety covalently bound to the anchor moiety, wherein the linker moiety is at least about 30 Å long and is entropically destabilized such that entropy of the linker moiety confers temperature-sensitive, conditional behavior upon the isolated nucleic acid target, and a test compound conjugated to the linker moiety. Each of the claimed elements is present in the artificial transcription factor taught by Stanojevic. With respect to the binding site, Stanojevic teaches non-peptidic DNA binding domains that are single stranded nucleic acid sequences (e.g., Table 1; paragraphs [0042], [0045] and [0066]). The claims do not limit the target nucleic acid sequence to a particular sequence for a specific sequence-specific transcription factor. The claims require the sequence to "define one and only one putative binding site for a sequence-specific regulatory factor." The single-stranded DNA taught by Stanojevic falls within the scope of a putative binding site for a sequence-specific transcription factor. Stanojevic teaches the use of one anchor moiety to covalently attach the single-stranded DNA to the flexible linker moiety.

The claims require that the linker is entropically destabilized so that the entropy confers temperature sensitive conditional behavior upon the isolated nucleic acid target. However, the specification does not provide a specific description of characteristics that an entropically destabilized linker would possess, except for length (see page 39, line 16 to page 40, line 6). Since Stanojevic teaches linkers of lengths that meet the claimed limitation of at least 30 Å in length, absent contrary evidence, the linkers would be entropically destabilized so that it would confer temperature sensitive conditional behavior on the nucleic acid target.

Regarding claim 35, Stanojevic teaches a kit comprising instructions and one or more containers holding a precursor composition having a flexible linker covalently bound to a DNA binding domain, where the precursor composition contains a reactive end group that can be used to couple the precursor compound to a test compound of interest (e.g., paragraph [0076]). Stanojevic teaches an artificial transcription factor that comprises a non-peptidic DNA binding domain, a flexible linker, and a transcriptional effector, one end of the linker being covalently bound to the DNA binding domain, and the other end of the linker being covalently bound to the transcriptional effector (e.g., paragraph [0011]). Further, Stanojevic teaches the further inclusion of one moiety that is a spacer or anchor molecule that allows the covalent attachment of the linker to the non-peptidic DNA binding domain (e.g., paragraphs [0063] and [0066]). Stanojevic teaches the artificial transcription factor where the linker is 10-100 Å, in the range of 25-40 Å, in the range of 40-60 Å, or in the range of 60-100 Å (e.g., paragraph [0011]). The rejected claim requires an isolated nucleic acid target that defines one and only one desired or putative binding site for a sequence-specific regulatory factor, excluding binding sites for transcriptional machinery, the isolated nucleic acid target having covalently bonded thereto, at a

point proximate to the binding site, one an only one anchor moiety, a linker moiety covalently bound to the anchor moiety, wherein the linker moiety is at least about 30 Å long and is entropically destabilized such that entropy of the linker moiety confers temperature-sensitive, conditional behavior upon the isolated nucleic acid target, and a test compound conjugated to the linker moiety. Each of the claimed elements is present in the artificial transcription factor taught by Stanojevic. With respect to the binding site, Stanojevic teaches non-peptidic DNA binding domains that are single stranded nucleic acid sequences (e.g., Table 1; paragraphs [0042], [0045] and [0066]). The single-stranded DNA taught by Stanojevic falls within the scope of the claimed nucleic acid target. Stanojevic teaches the use of one anchor moiety to covalently attach the single-stranded DNA to the flexible linker moiety.

Regarding claim 38, Stanojevic teaches a kit comprising instructions and one or more containers holding a precursor composition having a flexible linker covalently bound to a DNA binding domain, where the precursor composition contains a reactive end group that can be used to couple the precursor compound to a test compound of interest (e.g., paragraph [0076]). Stanojevic teaches an artificial transcription factor that comprises a non-peptidic DNA binding domain, a flexible linker, and a transcriptional effector, one end of the linker being covalently bound to the DNA binding domain, and the other end of the linker being covalently bound to the transcriptional effector (e.g., paragraph [0011]). Further, Stanojevic teaches the further inclusion of one moiety that is a spacer or anchor molecule that allows the covalent attachment of the linker to the non-peptidic DNA binding domain (e.g., paragraphs [0063] and [0066]). Stanojevic teaches the artificial transcription factor where the linker is 10-100 Å, in the range of 25-40 Å, in the range of 40-60 Å, or in the range of 60-100 Å (e.g., paragraph [0011]). The

rejected claim requires an isolated nucleic acid target that defines one and only one desired or putative binding site for a sequence-specific regulatory factor, excluding binding sites for transcriptional machinery, the isolated nucleic acid target having covalently bonded thereto, at a point proximate to the binding site, one an only one anchor moiety, a linker moiety covalently bound to the anchor moiety, wherein the linker moiety is at least about 30 Å long and is entropically destabilized such that entropy of the linker moiety confers temperature-sensitive, conditional behavior upon the isolated nucleic acid target, and a test compound conjugated to the linker moiety. Each of the claimed elements is present in the artificial transcription factor taught by Stanojevic. With respect to the binding site, Stanojevic teaches non-peptidic DNA binding domains that are single stranded nucleic acid sequences (e.g., Table 1; paragraphs [0042], [0045] and [0066]). The single-stranded DNA taught by Stanojevic falls within the scope of the claimed nucleic acid target. Stanojevic teaches the use of one anchor moiety to covalently attach the single-stranded DNA to the flexible linker moiety.

Response to Arguments - 35 USC § 102

The rejection of claims 1-3, 6-10, 32 and 36 under 35 U.S.C. 102(e) as being anticipated by Stanojevic has been withdrawn in view of Applicant's amendment to the claims in the reply filed 4/9/2009.

With respect to the rejection of claims 31, 34, 35 and 38 under 35 U.S.C. 102(e) as being anticipated by Stanojevic, Applicant's arguments filed 4/9/2009 have been fully considered but they are not persuasive.

The response notes that claims 31 and 34 have been amended to remove the recitation of a "desired" binding site for a sequence-specific regulatory factor and now recites that the isolated nucleic acid target "defines one and only one putative binding site for a sequence-specific regulatory factor." The response notes that the Merriam-Webster Online Dictionary defines the term "putative" as "commonly accepted or supposed" or "assumed to exist or to have existed." Thus, the response asserts that there is nothing ambiguous about the word "putative." Further, the response asserts that the single-stranded DNA taught by Stanojevic in Table 1 and paragraphs [0042], [0045] and [0066], as cited in the prior Office action, do not define an actual or even a putative binding site for a sequence-specific regulatory factor. The response points to the teachings of Stanojevic as describing the sequences as DNA-binding domains. Accordingly, the response asserts that Stanojevic does not disclose each of the claimed elements required by claims 31, 34, 35 and 38.

These arguments are not found persuasive. Stanojevic teaches nucleic acid sequences, which can be assumed to contain one an only one binding site for a sequence-specific regulatory factor. For example, SEQ ID NO: 5 contains one an only one putative binding site that is GTG-GGT-GGG. The prior art of record indicates that zinc finger proteins bind in a sequence-specific manner and can be made to bind a putative target site (e.g., Choo et al. PNAS, USA, pages 11168-11172, 1994, e.g., Figure 1; Choo et al. Curr. Opin. Struct. Biol., Vol. 10, pages 411-416, 2000; Greisman et al. Science, Vol. 275, pages 657-661, 1997; and Jamieson et al. Biochemistry, Vol. 33, pages 5689-5695, 1994, all references cited on the IDS filed 4/8/2004). The claims are not limited to any particular sequence for the nucleic acid target or to any specific sequence-specific regulatory factor, such that a specific sequence is required. Even though Stanojevic does

not describe the sequences as being putative binding sites, they fall within the scope of what is claimed for the reasons set forth above. The products taught by Stanojevic meet each of the structural limitations of the rejected claims.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 31, 32 and 34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Essigmann et al (US Patent No. 5,879,917; see the entire reference). This rejection was made in the Office action mailed 10/29/2008 and has been rewritten to address the amendments to the claims in the reply filed 4/9/2009.

Essigmann et al teach a composition comprising a heterobifunctional genotoxic compound, which comprises a transcription factor decoy that mimics the endogenous genomic binding site of a sequence specific transcription factor, said transcription factor decoy being covalently bound to a genotoxic agent through a linker (e.g., column 8, line 25 to column 14, line 61; column 23, line 12 to column 24, line 13). Further, Essigmann et al teach the inclusion of a crosslinking agent (anchor moiety) attached to the decoy molecule (e.g., column 21, lines 8-20). Essigmann et al teach the use of linkers that contain up to about 20 or 30 carbon atoms (e.g.,

column 23, lines 26-67). Essigmann et al teach the use of poly(ethyleneglycol) (PEG) as a linker (e.g., column 23, lines 36-40). A PEG linker of 20 or 30 carbons would be at least 30 Å long. Essigmann et al teach providing the abovementioned heterobifunctional genotoxic compound. Essigmann et al teach the use of the linker to space apart the binding moieties for the transcription factor decoy and genotoxic agent such that the heterobifunctional compound can sterically accommodate concurrent binding to the transcription factor and the cellular DNA (e.g., column 23, lines 40-44).

The claimed method recites that the linker is entropically destabilized so that the entropy confers temperature sensitive conditional behavior upon the isolated nucleic acid target. However, the specification does not provide a specific description of characteristics of an entropically destabilized linker would possess except for length (e.g., page 39, line 16 to page 40, line 6). Since Essigmann et al teach linkers of lengths that meet the claimed limitation of at least 30 Å in length, absent contrary evidence, the linkers would be entropically destabilized so that it would confer temperature sensitive conditional behavior on the nucleic acid target. As written the claim does not include a step that measures conditional behavior at different temperatures. With respect to the term "aptamer," the specification recognizes that the term "aptamer" generally refers to a double-stranded DNA or single-stranded RNA moiety that binds to a specific molecular target (see page 12, lines 13-15). However, the present specification defines the term "aptamer" to have a broader meaning encompassing a linker moiety that is dimensioned and configured to bind specifically with a small-molecule binding partner (see page 12, lines 15-18). The specification does not provide an explicit definition for the term, but indicates that it is broader than the definition usually given to the term. Accordingly, the term "aptamer" is

reasonably interpreted to encompass other linker structures that do not necessarily bind a small-molecule.

Essigmann et al do not specifically teach the molecule where one an only one anchor moiety is included between the binding site for the transcription factor and the linker.

It would have been obvious to one ordinary skill in the art to include an anchor moiety, which is a crosslinking agent, between the transcription factor binding site and the linker moiety, because Essigmann et al teach compositions comprising each of these components and teach that the compound should be designed to sterically accommodate concurrent binding to the transcription factor and the cellular DNA.

One would have been motivated to use one anchor moiety between the target sequence for the transcription factor and the linker to provide distance between the binding site and the linker so as to sterically accommodate transcription factor binding to the target sequence in the presence of the linker moiety. Based upon the teachings of the cited reference, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

With regard to claim 32, Essigmann et al teach the composition where the linker is a nucleic acid molecule. Essigmann et al do not explicitly teach the compound where the nucleic acid linker is an aptamer that binds a specific molecular target. However, Essigmann et al teach that aptamers are a class of nucleic acid agents, including RNA products that bind with high affinity to a desired ligand (e.g., column 21, lines 26-64). Because Essigmann et al teach the use of nucleic acid molecule linkers and teach that aptamers were known nucleic acid molecules, it

would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the aptamer for the linker in the compound of Essigmann et al.

Claims 35, 36 and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Essigmann et al (US Patent No. 5,879,917; see the entire reference) as applied to claims 31, 32 and 34 above, and further in view of Ahern (The Scientist, Vol. 9, No. 15, page 20, July 1995, printed as pages 1/7-7/7; see the entire reference). This rejection was made in the Office action mailed 10/29/2008 and is reiterated below. This rejection was made in the Office action mailed 10/29/2008 and has been rewritten to address the amendments to the claims in the reply filed 4/9/2009.

The teachings of Essigmann et al are described above and applied as before. Furthermore, Essigmann et al teach the use of numerous different genotoxic compounds that can be attached to the linker moiety of the compound (e.g., column 9, line 8 to column 11, line 43).

Essigmann et al do not teach providing a kit comprising instructions, and the compound where the genotoxic compound is not covalently attached to the linker, the compound being disposed in a suitable container.

Ahern teaches that products in kit form saves scientific investigators time and money (e.g., page 4/7, paragraph 2; page 5/7, paragraph 3). Ahern teaches that a kit can supply all of the necessary reagents for a particular research application and even provides detailed instructions (e.g., page 5/7, paragraph 3).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Essigmann et al to include the decoy-anchor-linker

compound in a container in kit form with instructions because Essigmann et al teach it is within the ordinary skill in the art to use numerous different genotoxic agents which can separately be selected from the disclosed agents for attachment to the linker and Ahern teaches the provision of reagents in kit form with instructions.

One would have been motivated to make such a modification in order to receive the expected benefit of saving an investigator time and money as taught by Ahern, by eliminating the need to synthesize the decoy-anchor-linker compound. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 1-3, 6-10, 13 and 15-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Essigmann et al (US Patent No. 5,879,917; see the entire reference) as applied to claims 31, 32 and 34 above, and further in view of Hunt et al (US Patent No. 5,859,226; see the entire reference). This rejection was made in the Office action mailed 10/29/2008 and has been rewritten to address the amendments to the claims in the reply filed 4/9/2009.

The teachings of Essigmann et al are described above and applied as before. Further, Essigmann et al teach that favorable properties of the decoy may be obtained by the use of nucleotide analogs or derivatives. Moreover, Essigmann et al teach the use of the linker to space apart the binding moieties for the transcription factor decoy and genotoxic agent such that the heterobifunctional compound can sterically accommodate concurrent binding to the transcription

factor and the cellular DNA and suggests the use of electrophoretic mobility shift assays to detect binding (e.g., column 23, lines 40-44; column 34, lines 58-65).

Essigmann et al do not teach the use of nucleotide analogs that are polyamides. Essigmann et al do not specifically teach the use of the electrophoretic mobility shift assay to evaluate whether the linked genotoxic compound alters binding of the transcription factor to its binding site in the decoy molecule.

Hunt et al teach decoy molecules that contain a substitution of conventional bases with analogous forms of sugars, pureness and pyrimdines (e.g., column 13, lines 33-47). Hunt et al teach that alternative backbone structures such as polyamide backbone are particularly advantageous (e.g., column 13, lines 43-47). Hunt et al teach that two types of gel shift assays can be used to study binding of a transcription factor to a decoy molecule: the direct binding assay and the competition assay (e.g., paragraph bridging columns 23-24). The direct binding assay tests whether or not a radiolabeled polynucleotide decoy is able to directly bind a transcription factor, and the competition assay tests whether a decoy is able to compete with a radiolabeled control sequence for transcription factor binding (e.g., paragraph bridging columns 23-24).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the heterobifunctional compound of Essigmann et al to include the polyamide backbone, taught by Hunt et al, at least between the binding site and the linker because Essigmann et al teaches the use of nucleotide analogs in a decoy, and Hunt et al teach it is within the ordinary skill in the art to use a polyamide backbone in a decoy. Further, it would have been obvious to one of ordinary skill in the art at the time the invention was made to assay

the heterobifunctional compound of Essigmann et al for binding to a sequence-specific transcription factor, whose binding site is present in the decoy, because Essigmann et al teach that the compound should be designed to sterically accommodate transcription factor binding and Hunt et al teach that gel shift assays test for transcription factor binding

One would have been motivated to make such a modification in order to receive the expected benefit of providing a compound with the advantageous properties of the polyamide as taught by Hunt et al. Furthermore, one would have been motivated to test the compound for binding to the transcription factor in a gel shift assay to test for any steric hindrance caused by the genotoxic moiety in order to evaluate whether the linked genotoxic compound alters binding of the transcription factor to its binding site in the decoy molecule. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent any evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Arguments - 35 USC § 103

With respect to the rejection of claims 31, 32 and 34 under 35 U.S.C. 103(a) as being unpatentable over Essigmann et al, Applicant's arguments filed 4/9/2009 have been fully considered but they are not persuasive.

The response asserts that Essigmann et al do not teach all the positively recited elements of claims 31 and 34. Specifically the response asserts that Essigmann et al do not teach an "anchor moiety" as defined by the claims. The response asserts that the crosslinking agents of Essigmann et al are disposed between a transcription factor and a transcription factor decoy and

not between a linker and a nucleic acid target. Further, the response asserts that Essigmann et al do not teach the anchor moiety proximate to the binding site.

These arguments are not found persuasive. The rejection of record indicates that Essigmann et al do not teach the compound where one an only one anchor moiety is included between the binding site for he transcription factor and the linker (e.g., Office action mailed 10/29/2008, page 18, last paragraph). However, given the teachings of Essigmann et al that it would be desirable to design the compound to sterically accommodate concurrent binding to the transcription factor and the cellular DNA, one would have been motivated to include an additional moiety between the target sequence for the transcription factor and the linker to provide distance between the binding site and the linker, so as to sterically accommodate transcription factor binding to the target sequence in the presence of the linker moiety (Office action mailed 10/29/2008, page 19, 1st and 2nd paragraphs). Although Essigmann et al do not exemplify the claimed compound of instant claims 31, 32 and 34, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include a moiety between the binding site and the linker to achieve the expected result of reducing steric hindrance for binding of the transcription factor. Essigmann et al teach the lengthening of the nucleotide sequence around the binding site (e.g., column 21, lines 8-20) and teach the lengthening of the linker (e.g., column 23, lines 26-67). Any portion of the nucleotide sequence between the binding site and linker can be considered the anchor. Alternatively, the first atom between the nucleic acid and second atom of the linker can be considered the anchor.

The response asserts that Essigmann et al do not teach a "test compound conjugated to the linker moiety" as recited in claims 31, 32 and 34. The response points to the specification at

page 26, lines 20-22, which state, "The test compound can be any moiety, without limitation, that is desired to be tested for its ability to modulate binding of regulatory factors to a nucleic acid target." The response assert that the genotoxic compound is not configured to test the role of the genotoxic agent in modulating binding of regulatory factors to a nucleic acid target. The response notes that the genotoxic compound is configured to bind cellular DNA to form a genomic lesion. The response asserts that Essigmann et al are completely silent with respect to affecting binding of regulatory factors to the genomic sites or even testing the binding of such regulatory factors.

These arguments are not found persuasive. The specification does not provide a limiting definition for the term "test compound." As noted in the response, the specification defines the term "test compound" to mean a compound of any structure. The fact that the specification states that the compound is selected based upon ones desire to test the compound for its ability to modulate does not limit the structure. The rejected claims are drawn to a product and not a method of testing binding. Thus, the genotoxic compound of Essigmann et al meets the structural limitations of the claims with regard to the "test compound." Even so, Essigmann et al are not completely silent with regard to testing the effect of the genotoxic compound on binding of a transcription factor to the linked target sequence. Essigmann et al suggest that the genotoxic compound and target sequence should be linked such that the compound could accommodate concurrent binding to the transcription factor and cellular DNA (e.g., column 23, lines 40-44). Thus, one may desire to test for the ability of the genotoxic compound to interfere with binding of the transcription factor to its target sequence in the compound. If the genotoxic compound

interferes with transcription factor binding then the compound of Essigmann et al would not serve its intended purpose.

The response asserts that the crosslinking agent would irreversibly link the transcription factor to the DNA sequence under transcription conditions, and the entire composition of Essigmann et al, as characterized by the Office, would not constitute a "test compound" as defined by Applicant.

This argument is not found persuasive. Claim 31 is drawn to a composition comprising an isolated nucleic acid target that defines one and only one putative binding site for a sequence-specific regulatory factor, excluding binding sites for transcriptional machinery, the isolated nucleic acid target having covalently bonded thereto, at a point proximate to the binding site, but not within the binding site, one an only one anchor moiety, a linker moiety covalently bonded to the anchor moiety, wherein the linker moiety is at least about 30 Å long and is entropically destabilized such that entropy of the linker moiety confers temperature-sensitive, conditional behavior upon the isolated nucleic acid target, and a test compound conjugated to the linker moiety. Claim 32 limits the linker to an aptamer. Claim 34 is drawn to the same compound as claim 31, except the claim does not specify that the anchor moiety is "not within the binding site" as recited in claim 31. Thus, the composition contains (i) an isolated nucleic acid target that contains one and only one putative binding site for a sequence-specific regulatory factor, (ii) an anchor moiety of any possible structure (specification, page 18, lines 7-11), (iii) a linker of any structure, as long as it is 30 Å long and is entropically destabilized, and (iv) a test compound of any structure (page 26, lines 20-23). As discussed in the rejection of record, Essigmann et al teach compositions comprising (i) a nucleic acid containing one and only one binding site for a

sequence-specific transcription factor; (ii) a linker that would meet the structural and functional limitations of the claims; and (iii) a genotoxic compound (test compound). Essigmann et al do not explicitly teach the use of an anchor moiety between the nucleic acid containing the target sequence, and the linker; however, Essigmann et al teaches it is within the skill of the art to make additional modifications to the composition (e.g., by adding a crosslinking agent). However, the rejection of record is not based upon the disclosed embodiment of Essigmann et al where a crosslinking agent is added within a target sequence. Rather, the rejection is based upon the teaching in Essigmann et al that the composition should be designed to allow concurrent binding of the genotoxic compound to the cellular DNA and the target sequence to the transcription factor (e.g., column 23, lines 40-44). In order for this to occur, one of skill in the art would have realized that increasing the distance between the target sequence and genotoxic compound may reduce steric hindrance and may prevent the genotoxic compound from inhibiting the binding of the sequence specific transcription factor. Thus, as discussed in the rejection of record, it would have been obvious to insert a moiety (any structure) between the nucleic acid containing the target sequence and the linker. Accordingly, the rejection of record addresses each of the limitations of the rejected claims.

For these reasons, and the reasons made of record in the previous office actions, the rejection is maintained.

With respect to the rejection of claims 35, 36 and 38 under 35 U.S.C. 103(a) as being unpatentable over Essigmann et al further in view of Ahern, Applicant's arguments filed 4/9/2009 have been fully considered but they are not persuasive.

The response asserts that Essigmann et al do not teach the compound where the anchor moiety is proximate to the binding site for a sequence-specific regulatory factor. Although, Essigmann et al do not exemplify this embodiment, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include a moiety of any structure (anchor) between the nucleic acid comprising the target sequence and the linker for the reasons of record and the reasons discussed above.

The response asserts that it would not have been obvious to provide the compound of Essigmann et al without the genotoxic compound. The response asserts that Essigmann et al and Ahern fail to provide any reason why using numerous different genotoxic agents that can be separately selected from the agents taught for attachment to the linker would be desired or beneficial. The response asserts that there is no motivation to make such a modification. Further, the response asserts that the Examiner has used hindsight reconstruction in making the rejection.

These arguments are not found persuasive. Essigmann et al specifically teach the attachment of different genotoxic agents to the linker (e.g., column 9, line 8 to column 11, line 43). Not including the genotoxic compound in the composition to allow one to add any one of a number of different options is not a product of innovation. Rather, it would have been a product of ordinary skill in the art at the time the invention was made and common sense. One would have been motivated to have a partially built structure, which could be used to add any number of different genotoxic compounds. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight

reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In the instant case, Essigmann et al demonstrate it is within the skill of the art to make the compositions, and teach the different components that may be combined. The rejection of record, based upon the synthesis of a partial structure, relies only upon common sense and the knowledge which was within the level of ordinary skill in the art at the time the invention was made.

The rejection of claim 4 under 35 U.S.C. 103(a) as being unpatentable over Essigmann et al further in view of Hunt et al is moot in view of Applicant's cancellation of the claim in the reply filed 4/9/2009.

With respect to the rejection of claims 1-3, 6-10, 13 and 15-19 under 35 U.S.C. 103(a) as being unpatentable over Essigmann et al further in view of Hunt et al, Applicant's arguments filed 4/9/2009 have been fully considered but they are not persuasive.

The response asserts that Essigmann et al do not teach all the positively recited elements of the claims. Specifically the response asserts that Essigmann et al do not teach an "anchor moiety" as defined by the claims. The response asserts that the crosslinking agents of Essigmann et al are disposed between a transcription factor and a transcription factor decoy and not between a linker and a nucleic acid target. Further, the response asserts that Essigmann et al do not teach the anchor moiety proximate to the binding site.

These arguments are not found persuasive. The rejection of record indicates that Essigmann et al do not teach the compound where one an only one anchor moiety is included

between the binding site for he transcription factor and the linker (e.g., Office action mailed 10/29/2008, page 18, last paragraph). However, given the teachings of Essigmann et al that it would be desirable to design the compound to sterically accommodate concurrent binding to the transcription factor and the cellular DNA, one would have been motivated to include an additional moiety between the target sequence for the transcription factor and the linker to provide distance between the binding site and the linker, so as to sterically accommodate transcription factor binding to the target sequence in the presence of the linker moiety (Office action mailed 10/29/2008, page 19, 1st and 2nd paragraphs). Although Essigmann et al do not exemplify the claimed compound, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include a moiety between the binding site and the linker to achieve the expected result of reducing steric hindrance for binding of the transcription factor. Essigmann et al teach the lengthening of the nucleotide sequence around the binding site (e.g., column 21, lines 8-20) and teach the lengthening of the linker (e.g., column 23, lines 26-67). Any portion of the nucleotide sequence between the binding site and linker can be considered the anchor. Alternatively, the first atom between the nucleic acid and second atom of the linker can be considered the anchor.

The response asserts that the crosslinking agent would irreversibly link the transcription factor to the DNA sequence under transcription conditions, and the entire composition of Essigmann et al, as characterized by the Office, would not constitute a "test compound" as defined by Applicant.

This argument is not found persuasive. The claims require a composition comprising an isolated nucleic acid target that defines one and only one putative binding site for a sequence-

specific regulatory factor, excluding binding sites for transcriptional machinery, the isolated nucleic acid target having covalently bonded thereto, at a point proximate to the binding site, but not within the binding site, one an only one anchor moiety, a linker moiety covalently bonded to the anchor moiety, wherein the linker moiety is at least about 30 Å long and is entropically destabilized such that entropy of the linker moiety confers temperature-sensitive, conditional behavior upon the isolated nucleic acid target, and a test compound conjugated to the linker moiety. Thus, the composition contains (i) an isolated nucleic acid target that contains one and only one putative binding site for a sequence-specific regulatory factor, (ii) an anchor moiety of any possible structure (specification, page 18, lines 7-11), (iii) a linker of any structure, as long as it is 30 Å long and is entropically destabilized, and (iv) a test compound of any structure (page 26, lines 20-23). As discussed in the rejection of record, Essigmann et al teach compositions comprising (i) a nucleic acid containing one and only one binding site for a sequence-specific transcription factor; (ii) a linker that would meet the structural and functional limitations of the claims; and (iii) a genotoxic compound (test compound). Essigmann et al do not explicitly teach the use of an anchor moiety between the nucleic acid containing the target sequence, and the linker; however, Essigmann et al teaches it is within the skill of the art to make additional modifications to the composition (e.g., by adding a crosslinking agent). However, the rejection of record is not based upon the disclosed embodiment of Essigmann et al where a crosslinking agent is added within a target sequence. Rather, the rejection is based upon the teaching in Essigmann et al that the composition should be designed to allow concurrent binding of the genotoxic compound to the cellular DNA and the target sequence to the transcription factor (e.g., column 23, lines 40-44). Essigmann et al suggest the use of electrophoretic mobility shift assays

to detect binding (e.g., column 23, lines 40-44; column 34, lines 58-65). In order for this to occur, one of skill in the art would have realized that increasing the distance between the target sequence and genotoxic compound may reduce steric hindrance and may prevent the genotoxic compound from inhibiting the binding of the sequence specific transcription factor. Accordingly, assay of Essigmann et al and Hunt et al would not result in irreversible binding of transcription factor under "transcription conditions."

The rejection of claims 1-3 and 6-10 under 35 U.S.C. 103(a) as being unpatentable over Ansari et al (2001) in view of Aurora et al (2002) has been withdrawn in view of Applicant's amendment to the claims in the reply filed 4/9/2009.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is 571-272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Examiner
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/JD/

/ Christopher S. F. Low /
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